BRIEF COMMUNICATION

Allium Vegetables and Risk of Prostate Cancer: A Population-Based Study

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Epidemiologic and laboratory studies suggest that allium vegetables and garlic constituents have antitumor effects. In a population-based, case–control study conducted in Shanghai, China, we investigated the association between intake of allium vegetables, including garlic, scallions, onions, chives, and leeks, and the risk of prostate cancer. We administered in-person interviews and collected information on 122 food items from 238 case subjects with incident, histologically confirmed prostate cancer and from 471 male population control subjects. Men in the highest of three intake categories of total allium vegetables (>10.0 g/day) had a statistically significantly lower risk (odds ratio [OR] = 0.51, 95% confidence interval [CI] = 0.34 to 0.76; P_{trend}<.001) of prostate cancer than those in the lowest category (<2.2 g/day). Similar comparisons between categories showed reductions in risk for men in the highest intake categories for garlic (OR = 0.47, 95% CI = 0.31 to 0.71; P_{trend}<.001) and scallions (OR = 0.30, 95% CI = 0.18 to 0.51; P_{trend}<.001). The reduced risk of prostate cancer associated with allium vegetables was independent of body size, intake of other foods, and total calorie intake and was more pronounced for men with localized than with advanced prostate cancer. [J Natl Cancer Inst 2002;94:1648–51]

Although epidemiologic studies have related consumption of allium vegetables to lower risks for cancers of the stomach, colon, esophagus, and perhaps breast *(1–9),* few data are available on a possible association with prostate cancer. Allium vegetables, including garlic, onions, leeks, chives, scallions, and shallots, are rich in flavonols and organosulfur compounds, which have tumor-inhibitory properties in laboratory studies *(1,2,10–14).* The precise mechanisms are unclear, although some components of allium vegetables are reported to block metabolism of polycyclic hydrocarbons and nitrosamines, inhibit microbial activity and enhance immunocompetence, suppress cell division and proliferation, modulate phase I and II enzymes and DNA repair, or induce apoptosis *(11).* In addition, a recent study *(4)* has shown that the garlic constituent *S*-allylmercaptocysteine can alter androgenic action in prostatic cells by modulating the expression of androgen-responsive biomarkers. However, whether allium vegetables influence the risk of prostate cancer *in vivo* is unclear.

As part of a population-based, case–control study conducted in Shanghai, we report herein the relationship between allium vegetable intake and the risk of prostate cancer. The methods of this study have been described in detail elsewhere *(15–18).* Briefly, case subjects with histologically confirmed incident prostate cancer diagnosed between 1993 and 1995 were identified through a rapid reporting system. Two hundred thirty-eight (89%) of 268 eligible case subjects (representing 95% of the case subjects diagnosed in Shanghai during the study period) were interviewed for this study. On the basis of a resident registry of all persons aged 16 years and older in urban Shanghai, healthy men were randomly selected from the 6.5 million permanent residents and frequency-matched to the case subjects' expected age distribution in 5-year age groups. Of the 495 eligible population control subjects, 471 (95%) were interviewed for this study. The study was approved by the Institutional Review Boards of the U.S. National Cancer Institute and the Shanghai Cancer Institute (Shanghai, China). All study participants provided written informed consent.

Trained interviewers used a structured questionnaire to obtain information on epidemiologic factors from study participants. Usual adult dietary intake [in liangs; one liang equals 50 grams *(19)*] 5 years before the date of the interview was assessed with the use of a 122-item food-frequency instrument listing foods most frequently consumed by Shanghai residents. This instrument was validated by 24-hour dietary recall methods (Gao YT: unpublished data). The 122 food items were combined into 20 food groups, including the allium vegetable food group (i.e., garlic, scallions, onions, leeks, and Chinese chives). Nutrient values were derived using the Chinese Food Composition Tables *(19),* and total energy intake was derived by summing the caloric contents from all foods. Correlations of intake of allium vegetables with each other and with other foods were assessed using Spearman rank-order correlation coefficients. Unconditional logistic regression was used to generate odds ratios (ORs) and 95% confidence intervals (CIs) to estimate the effects of allium vegetable consumption on the risk of prostate cancer independent of other potential risk factors (including age at interview, total energy intake, alcohol use, and intake of total vegetables and meats) *(20).* Allium vegetable intake was divided into three groups of roughly equal size on the basis of tertiles of intake among population control subjects; however, because study participants reported intake in integer values of liangs, clustering prevented uniform numbers of subjects in each category. Tests for linear trend were performed using approximate tertiles as consecutive integers (continuous variables). Statistical analyses were performed using SAS, version 8 (SAS Institute, Inc., Cary, NC). All statistical tests were two-sided.

We first compared the demographic characteristics of the control subjects with those of the case subjects and found that the case subjects were slightly better educated, were less likely to be married, and had a higher waist-to-hip ratio. About two thirds of the case subjects were diagnosed with advanced [clinical

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stage C or D *(21)*] versus localized (stage A or B) prostate cancer, and two thirds of the case subjects were diagnosed with prostate cancers that were moderately or poorly differentiated. At the time of diagnosis, most case subjects had symptoms of their disease, with 77% having serum prostate-specific antigen levels of greater than 10 ng/mL (median = 87 ng/mL).

For the 471 control subjects, the median intake of allium vegetables was 5.5 g/day (about 2 cloves of garlic). Among the control subjects reporting any allium vegetable consumption (88%), the median intake was 8.3 g/day. Garlic was the most commonly consumed allium vegetable, followed by scallions and Chinese chives (medians, 5.9, 2.6, and 2.5 g/day, respectively). Consumption of allium vegetables was positively and statistically significantly correlated with total fat, total calories, animal fat, all vegetables combined, cruciferous vegetables, green leafy vegetables, dark orange vegetables, and phytoestrogen-containing foods (Table 1). In addition, the five individual allium vegetables were strongly and statistically significantly correlated with one another (Table 1).

After adjusting for age and total caloric intake, we determined whether the consumption of allium vegetables was associated with a reduced risk of prostate cancer (Table 2) and found that men who consumed more than 10.0 g/day of allium vegetables had a reduced risk of prostate cancer compared with those who consumed less than 2.2 g/day (OR = 0.51, 95% CI = 0.34 to 0.76; P_{trend}<.001). Similar results were observed for allium vegetables when the referent category included only men with no intake (data not shown). Garlic and scallions had the most pronounced effect on the risk reductions. Men in the highest intake categories of chives and onions experienced nonsignificant risk reductions. Compared with control subjects, the reduced risk of prostate cancer associated with higher consumption of allium vegetables was more pronounced for patients with localized prostate cancer than for those with advanced cancer (Table 2).

Although fruits and vegetables have been inconsistently related to a reduced risk of prostate cancer *(22),* one study *(23)* reported that intake of two or more servings of garlic per week was associated with a statistically nonsignificant 36% reduction in risk of prostate cancer. In our study population, although intake of fruits and vegetables was associated with a slight reduction in prostate cancer risk (Hsing AW, Gridley G, Gao YT, Deng J, Madigan MP, Sesterhenn I, et al.: unpublished data), the reduced risk of prostate cancer associated with consumption of allium vegetables was much more pronounced than the effects of other individual vegetables or vegetable groups. Although consumption of allium vegetables was positively correlated with consumption of several other dietary items in our study, the reduced risk of prostate cancer associated with allium vegetable intake persisted after adjustment for these dietary items. Furthermore, although reduced risks associated with intake of lycopene and cruciferous vegetables have been reported for prostate cancer in Western populations *(24–26),* no such association was found in our study of Chinese men. Nevertheless, it is possible that the inverse association we observed between prostate cancer and allium vegetable intake may be a result of uncontrolled confounding by some unidentified or unmeasured factors.

In our study, garlic and scallions were the major allium vegetables associated with a reduced prostate cancer risk, perhaps a result of their more frequent consumption in the Shanghai population. Although reported consumption of onions is higher in Western populations *(27)* than in China, garlic intake in our study was higher than in U.S. and British population studies *(23,28).* In our study in Shanghai, 46% of the population control subjects reported consuming at least 6 grams (about 2 cloves) of garlic per week. By contrast, only 15% of British males re-

Table 1. Spearman's rank-order correlation coefficients between intake of allium vegetables and various nutrients among 471 male population control subjects from Shanghai, China

	Allium	Garlic	Scallions	Onions	Chinese chives	Leeks
Allium	1.0					
Garlic	0.81 *P*<.001	1.0				
Scallions	0.61 *P*<.001	0.41 *P*<.001	1.0			
Onions	0.60 *P*<.001	0.51 *P*<.001	0.49 *P*<.001	1.0		
Chinese chives	0.69 *P*<.001	0.48 *P*<.001	0.34 *P*<.001	0.46 *P*<.001	1.0	
Leeks	0.46 *P*<.001	0.38 *P*<.001	0.38 *P*<.001	0.46 *P*<.001	0.46 *P*<.001	1.0
Total calories	0.17 *P*<.001	0.17 *P*<.001	0.02* 	0.10 *P* = .04	0.24 *P*<.001	0.19 *P*<.001
Total fat	0.17 *P*<.001	0.09 *P* = .04	0.08* 	0.13 *P* = .01	0.17 *P*<.001	–0.02*
Animal fat	0.15 *P*<.001	0.07* 	0.16* 	0.11 *P* = .02	0.11 *P* = .02	–0.04*
Red meat	0.11 *P* = .01	0.06* 	0.18 *P*<.001	0.12 *P* = .01	0.10 *P* = .04	0.01*
Poultry	0.10 *P* = .03	0.06* 	0.12 *P* = .01	0.10 *P* = .03	0.11 *P* = .02	–0.03*
Animal foods	0.08*	–0.02*	0.08*	0.06*	0.09*	–0.003*
Soy	0.07*	0.02*	0.06*	0.09*	0.07*	0.01*
Phytoestrogen-containing foods†	0.23 *P*<.001	0.15 *P*<.001	0.10 *P* = .02	0.17 *P*<.001	0.25 *P*<.001	0.16 *P*<.001
Legumes other than soybeans	0.12 *P* = .01	0.04* 	0.03* 	0.13 *P* = .004	0.21 *P*<.001	0.20 *P*<.001
Cruciferous vegetables	0.17 *P*<.001	0.07* 	0.15 *P*<.001	0.08*	0.16 *P*<.001	0.06*
Green leafy vegetables	0.19 *P*<.001	0.11 *P* = .02	0.12 *P* = .01	0.11 *P* = .02	0.22 *P*<.001	0.08*
Dark orange vegetables	0.26 *P*<.001	0.19 *P*<.001	0.26 *P*<.001	0.27 *P*<.001	0.26 *P*<.001	0.07*
Tomatoes	0.004*	–0.02*	0.05*	0.12 *P* = .01	0.14 *P* = .002	0.07*
All vegetables	0.27 *P*<.001	0.18 *P*<.001	0.15 *P*<.001	0.19 *P*<.001	0.29 *P*<.001	0.19 *P*<.001

*Nonsignificant at $P = .05$ level. All statistical tests were two-sided.

†Includes food such as Chinese cabbage, wax gourds, soy milk, tofu, and bok choy.

Table 2. Odds ratios* (ORs) and 95% confidence intervals (CIs) for the risk of prostate cancer in relation to consumption of allium vegetables, by extent of disease in men from Shanghai, China

		Control subjects (n = 471)	All case subjects (n = 238)		Case subjects with localized disease (n = 79)		Case subjects with advanced disease (n = 152)	
Allium vegetables	(g/day)†	n	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Allium food group	<2.2	152	98	1.0 (–)‡	39	1.0 (–)	57	1.0 (–)
	2.2–10.0	161	85	0.79 (0.54 to 1.14)	25	0.58 (0.33 to 1.01)	56	0.89 (0.58 to 1.37)
	>10.0	158	55	0.51 (0.34 to 0.76)	15	0.34 (0.18 to 0.66)	39	0.61 (0.38 to .98)
				P_{trend}<.001§		P_{trend}<.001		P_{trend} = .04
Garlic	0	180	106	1.0 (–)	42	1.0 (–)	62	1.0 (–)
	0.01–2.14	132	86	1.06 (0.74 to 1.53)	24	0.74 (0.42 to 1.30)	59	1.25 (0.82 to 1.91)
	>2.14	159	46	0.47 (0.31 to 0.71)	13	0.33 (0.17 to 0.65)	31	0.53 (0.33 to 0.87)
				P_{trend}<.001		P_{trend}<.001		P_{trend} = .02
Scallions	0	267	164	1.0 (–)	63	1.0 (–)	96	1.0 (–)
	0.1–2.14	103	55	0.84 (0.57 to 1.23)	12	0.48 (0.25 to 0.93)	41	1.07 (0.69 to 1.65)
	>2.14	101	19	0.30 (0.18 to 0.51)	4	0.17 (0.06 to 0.47)	15	0.41 (0.23 to 0.74)
				P_{trend}<.001		P_{trend}<.001		P_{trend} = .01
Chinese chives	<0.41	154	19	1.0 (–)	28	1.0 (–)	49	1.0 (–)
	0.41–2.19	207	109	1.00 (0.70 to 1.43)	37	0.95 (0.55 to 1.63)	69	1.00 (0.65 to 1.54)
	>2.19	110	50	0.83 (0.53 to 1.29)	14	0.66 (0.33 to 1.34)	34	0.89 (0.53 to 1.50
				P_{trend} = .44		P_{trend} = .27		P_{trend} = .69
Leeks	0	275	118	1.0 (–)	48	1.0 (–)	68	1.0 (–)
	0.01–2.72	132	88	1.52 (1.07 to 2.15)	27	1.13 (0.67 to 1.91)	58	1.73 (1.15 to 2.62)
	>2.72	64	32	1.09 (0.67 to 1.78)	4	0.33 (0.11 to 0.97)	26	1.54 (0.90 to 2.64)
				P_{trend} = .22		P_{trend} = .14		P_{trend} = .03
Onion	0	177	81	1.0 (–)	30	1.00 (–)	49	1.0 (–)
	0.01–1.66	111	95	1.85 (1.27 to 2.72)	32	1.69 (0.97 to 2.94)	58	1.87 (1.19 to 2.94)
	>1.66	183	62	0.71 (0.48 to 1.06)	17	0.53 (0.28 to 1.00)	45	0.85 (0.54 to 1.35)
				P_{trend} = .12		P_{trend} = .07		P_{trend} = 0.50

*Adjusted for age and total calories.

†Allium vegetable intake divided approximately into tertile-based percentile distributions among population control subjects; clustering of reported intake prevented uniform numbers of subjects in each category.

‡Referent group.

§*P* for linear trend.

ported eating at least two servings (~6 grams) of garlic per week *(23),* and just 20% of U.S. women consumed at least one serving (~3 grams) per week *(28).*

There are several potential limitations to our study. The imprecise nature of dietary assessments based on self-reported food frequency data is likely to have resulted in some misclassification of allium intake, which is unlikely to differ between case and control subjects. However, differential recall of allium vegetable intake between case and control subjects, although possible, may have been lessened by obtaining information on usual adult intake 5 years before interview, by a lack of evidence that study participants were aware of any potential link between allium vegetable intake and prostate cancer, and by the small proportion of case subjects (<10%) reporting recent changes in dietary habits that might have influenced recall of usual dietary intake. It is unlikely that having prostate cancer substantially influenced case subjects' current allium vegetable intake or their recall of usual intake 5 years before the interview, since the mean reported intake did not differ substantially between case subjects with localized versus advanced stage prostate cancer. Although heating and cooking may reduce the tumor-inhibitory properties of allium vegetables *(29),* we do not have data on these factors.

In summary, our population-based, case–control study of the risk of prostate cancer in Chinese men identified a reduced risk associated with consumption of allium vegetables, especially garlic and scallions, that was independent of intake of other dietary items. Further studies, especially cohort investigations in Western and Asian populations, are needed to clarify the reduced risks associated with specific allium vegetables and to determine the biologic mechanisms involved.

REFERENCES

(1) Fleischauer AT, Poole C, Arab L. Garlic consumption and cancer prevention: meta-analyses of colorectal and stomach cancers. Am J Clin Nutr 2000;72:1047–52.

(2) Milner JA. A historical perspective on garlic and cancer. J Nutr 2001;131:1027S-31S.

(3) Fleischauer AT, Arab L. Garlic and cancer: a critical review of the epidemiologic literature. J Nutr 2001;131:1032S–40S.

(4) Pinto JT, Qiao C, Xing J, Suffoletto BP, Schubert KB, Rivlin RS, et al. Alterations of prostate biomarker expression and testosterone utilization in human LNCaP prostatic carcinoma cells by garlic-derived S-allylmercaptocysteine. Prostate 2000;45:304–14.

(5) Dorant E, van den Brandt PA, Goldbohm RA, Sturmans F. Consumption of onions and a reduced risk of stomach carcinoma. Gastroenterology 1996;110:12–20.

(6) You WC, Zhang L, Gail MH, Ma JL, Chang YS, Blot WJ, et al. Helicobacter pylori infection, garlic intake and precancerous lesions in a Chinese population at low risk of gastric cancer. Int J Epidemiol 1998;27:941–4.

(7) Gao CM, Takezaki T, Ding JH, Li MS, Tajima K. Protective effect of allium vegetables against both esophageal and stomach cancer: a simultaneous case-referent study of a high-epidemic area in Jiangsu Province, China. Jpn J Cancer Res 1999;90:614–21.

(8) Challier B, Perarnau JM, Viel JF. Garlic, onion and cereal fibre as protective factors for breast cancer: a French case-control study. Eur J Epidemiol 1998;14:737–47.

(9) You WC, Blot WJ, Chang YS, Ershow A, Yang ZT, An Q, et al. Allium vegetables and reduced risk of stomach cancer. J Natl Cancer Inst 1989;81:162–4.

(10) Fenwick GR, Hanley AB. The genus Al-

lium—Part 1. Crit Rev Food Sci Nutr 1985; 22:199–271.
(11) Milner JA. Mechanisms by which garlic and allyl sulfur compounds suppress carcinogen bioactivation. Garlic and carcinogenesis. Adv Exp Med Biol 2001;492:69–81.
(12) Fukushima S, Takada N, Hori T, Wanibuchi H. Cancer prevention by organosulfur compounds from garlic and onion. J Cell Biochem Suppl 1997;27:100–5.
(13) Welch C, Wuarin L, Sidell N. Antiproliferative effect of the garlic compound S-allyl cysteine on human neuroblastoma cells in vitro. Cancer Lett 1992;63:211–9.
(14) Ali M, Thomson M, Afzal M. Garlic and onions: their effect on eicosanoid metabolism and its clinical relevance. Prostaglandins Leukot Essent Fatty Acids 2000;62:55–73.
(15) Hsing AW, Gao YT, Wu G, Wang X, Deng J, Chen YL, et al. Polymorphic CAG and GGN repeat lengths in the androgen receptor gene and prostate cancer risk: a population-based case-control study in China. Cancer Res 2000;60:5111–6.
(16) Hsing AW, Deng J, Sesterhenn IA, Mostofi FK, Stanczyk FZ, Benichou J, et al. Body size and prostate cancer: a population-based case-control study in China. Cancer Epidemiol Biomarkers Prev 2000;9:1335–41.
(17) Hsing AW, Chua S Jr, Gao YT, Gentzschein E, Chang L, Deng J, et al. Prostate cancer risk and serum levels of insulin and leptin: a population-based study. J Natl Cancer Inst 2001;93:783–9.
(18) Hsing AW, Chen C, Chokkalingam AP, Gao YT, Dightman DA, Nguyen HT, et al. Polymorphic markers in the SRD5A2 gene and prostate cancer risk: a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2001;10:1077–82.
(19) Chinese Academy of Medical Sciences. Food composition tables (in Chinese). Beijing: People's Health Publishing House; 1991.
(20) Breslow NE, Day NE. Statistical methods in cancer research. Volume I. The analysis of case-control studies. IARC Sci Publ 1980;32: 5–338.
(21) Jewett HJ. The present status of radical prostatectomy for stages A and B prostatic cancer. Urol Clin North Am 1975;2:105–24.
(22) Chan JM, Giovannucci EL. Vegetables, fruits, associated micronutrients, and risk of prostate cancer. Epidemiol Rev 2001;23: 82–6.
(23) Key TJ, Silcocks PB, Davey GK, Appleby PN, Bishop DT. A case-control study of diet and prostate cancer. Br J Cancer 1997;76: 678–87.
(24) Kolonel LN, Hankin JH, Whittemore AS, Wu AH, Gallagher RP, Wilkens LR, et al. Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. Cancer Epidemiol Biomarkers Prev 2000;9:795–804.
(25) Giovannucci E, Clinton SK. Tomatoes, lycopene, and prostate cancer. Proc Soc Exp Biol Med 1998;218:129–39.
(26) Cohen JH, Kristal AR, Stanford JL. Fruit and vegetable intakes and prostate cancer risk. J Natl Cancer Inst 2000;92:61–8.
(27) Dorant E, van den Brandt PA, Goldbohm RA. Allium vegetable consumption, garlic supplement intake, and female breast carcinoma incidence. Breast Cancer Res Treat 1995;33:163–70.
(28) Steinmetz KA, Kushi LH, Bostick RM, Folsom AR, Potter JD. Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. Am J Epidemiol 1994;139:1–15.
(29) Song K, Milner JA. Heating garlic inhibits its ability to suppress 7,12- dimethylbenz(a)anthracene-induced DNA adduct formation in rat mammary tissue. J Nutr 1999;129: 657–61.

NOTES

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